

Remarks/Arguments

The foregoing amendments to the claims are of formal nature, and do not add new matter. Claims 119-127 and 129-131 are pending in this application and are rejected on various grounds. Claims 119-120 have been canceled without prejudice or disclaimer. The rejections to the presently pending claims are respectfully traversed.

Claim Rejections – 35 USC § 101 and 112, first paragraph

Claims 119-131 remain rejected under 35 U.S.C. §101 allegedly “because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.”

Claims 119-131 remain further rejected under 35 U.S.C. §112, first paragraph allegedly “since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention”.

The Examiner maintains her previous rejections that PRO1185 polypeptides lack utility because “(i)ncreased copy number of DNA does not provide a readily apparent use for the polypeptide, for which there is no information regarding level of expression, activity or role in cancer. the specification fails to teach that PRO1185 protein levels increase”. The Examiner maintains that, given the disclosure in the art, such as Pennica *et al.*, Konopka *et al.*, and Haynes *et al.*, there is not always such a correlation, the skilled artisan would not assume it is so, but would perform the experiment to verify it.” Applicants respectfully traverse.

Arguments

Based on the arguments presented in the previous responses, Applicants maintain that a *prima facie* case has not been made for lack of utility by the Examiner and that the specification provides sufficient disclosure to establish a specific, substantial and credible utility for the PRO1185 polypeptide of SEQ ID NO:401 and other native polypeptides with 90-99% identity to the PRO1185 polypeptide. In particular, it is maintained that the gene amplification assay discloses that the nucleic acid encoding PRO1185 is significantly overexpressed in human tumor tissues as compared to a non-cancerous human tissue control. In support of their showing that the gene amplification values for the nucleic acids encoding PRO1185 are significant, Applicants

submit herewith, a Declaration by Dr. Audrey D. Goddard. Consideration of this Declaration is respectfully requested. No new matter is added by way of this submission. Applicants particularly draw the Examiner's attention to page 3 of the Goddard Declaration which clearly states that:

It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.*, non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy (Emphasis added).

Accordingly, the 21.01, 21.66 2 1.58- fold amplification or **2.013, 3.160 and 2.989-fold** amplification in lung or colon tumors would be considered significant and credible by one skilled in the art, based upon the facts disclosed in the Goddard Declaration.

Further, Applicants respectfully maintain that, for the reasons previously set forth in the Applicants' responses, that in general, one skilled in the art would expect protein expression to increase with gene amplification increases. Applicants submit that the references Pennica *et al.*, Konopka *et al.* and Haynes do not show that a lack of correlation between gene (DNA) amplification and elevated mRNA levels, in general, exists. Further, Applicants have submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will also be expressed at an elevated level. First, the articles by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* (submitted with Applicants' Response filed June 22, 2004) collectively teach that in general, gene amplification increases mRNA expression. Applicants further submitted that, even if there were no correlation between gene amplification and increased mRNA/protein expression, (which Applicants expressly do not concede), a polypeptide encoded by an amplified gene in cancer would **still** have a specific, substantial, and credible utility as explained below. The Declaration of Dr. Avi Ashkenazi had supporting evidence for such a utility in a real-world example (the HER-2/ Neu example) presented in an article by

Hanna and Mornin (both submitted with Applicants' Response filed June 22, 2004). The article supported the view that, even when the protein is not over-expressed, an assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it. Thus, as evidenced by the Ashkenazi Declaration and the teachings of Hanna and Mornin, one skilled in the art would appreciate that simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, were not over-expressed. This leads to better determination of a suitable therapy for the tumor. Thus, the gene amplification data demonstrates that the PRO1185 polypeptide of the present invention is also useful as a diagnostic marker for the presence of one or more lung tumors in which the encoding DNA is significantly overexpressed.

Thus, Applicants have demonstrated utility for the PRO1185 polypeptide as a marker for adenocarcinomas of the lung or colon. Accordingly, the present 35 U.S.C. §101 and §112, first paragraph utility rejections should be withdrawn.

Claim Rejections – 35 USC § 112, first paragraph- written description

Claims 119-123 are further rejected under 35 U.S.C. §112, first paragraph allegedly "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed. In particular, the PTO alleges that "[t]he claims do not require that polypeptide possess any particular biological activity, nor any particular conserved structure, nor other disclosed distinguishing feature. Thus, the claims are drawn to a genus of polypeptides that is defined only by sequence identity." Applicants respectfully disagree for the reasons cited below.

The Legal Test for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph is "whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter, rather than the presence or absence of literal support in the

specification for the claim language.¹ The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis.² The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure.^{3,4}

In *Environmental Designs, Ltd. v. Union Oil Co.*,⁵ the Federal Circuit held, "Factors that may be considered in determining level of ordinary skill in the art include (1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field." (Emphasis added).⁶ Further, The "hypothetical 'person having ordinary skill in the art' to which the claimed subject matter pertains would, of necessity have the capability of understanding the scientific and engineering principles applicable to the pertinent art."^{7,8}

The Examiner directed Applicants to the Guidelines for the Examination of Patent Applications under the 35 U.S.C. 112, first paragraph "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-111, Friday, January 5, 2001. However, Example 14 of the Synopsis of Application of Written Description Guidelines issued by the U.S. Patent Office clearly states that the protein variants meet the requirements of 35 U.S.C. §112, first paragraph, as providing adequate written description for the claimed invention even if the

¹ *In re Kaslow*, 707 F.2d 1366, 1374, 212 USPQ 1089, 1096 (Fed. Cir. 1983).

² See also *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991).

³ *Union Oil v. Atlantic Richfield Co.*, 208 F.2d 989, 996 (Fed. Cir. 2000).

⁴ See also M.P.E.P. §2163 II(A).

⁵ 713 F.2d 693, 696, 218 USPQ 865, 868 (Fed. Cir. 1983), *cert. denied*, 464 U.S. 1043 (1984).

⁶ See also M.P.E.P. §2141.03.

⁷ *Ex parte Hiyamizu*, 10 USPQ2d 1393, 1394 (Bd. Pat. App. & Inter. 1988) (emphasis added).

⁸ See also M.P.E.P. §2141.03.

specification contemplates but does not exemplify variants of the protein if (1) the procedures for making such variant proteins is routine in the art, (2) the specification provides an assay for detecting the functional activity of the protein and (3) the variant proteins possess the specified functional activity and at least 95% sequence identity to the reference sequence.

The Disclosure Provides Sufficient Written Description for the Claimed Invention

Claims 119-120 have been canceled without prejudice or disclaimer and hence this rejection is rendered moot for these claims. Applicants respectfully submit that amended Claims 121 -123 are not “defined only by sequence identity.” Instead, they recite a specific, functional recitation that the nucleic acid encoding the “native sequence” polypeptides are overexpressed in lung or colon tumors, that is, are directed to a genus of native sequence polypeptides that are at least 90-99% identical to SEQ ID NO:401. Specifically, Example Example 170, page 539 sets forth a gene amplification method and provides step-by-step guidelines and protocols for gene amplification assays for determining whether a gene which encodes for the native polypeptide having at least 90% identity to PRO1185 is overexpressed in colon or lung tumors. Applicants submit that the instant specification evidences the actual reduction to practice of a full-length PRO1185 polypeptide of SEQ ID NO:401, with or without its signal sequence. Thus, the genus of native polypeptides with at least 90% sequence identity to SEQ ID NO:401, which possess the functional property of having a nucleic acid which is overexpressed in colon or lung tumors” would clearly meet the requirement of 35 U.S.C. §112, first paragraph, as providing adequate written description.

Further, Applicants point out that the instant specification clearly describes methods for the determination of percent identity between two amino acid sequence (See pages 306-308, line 14 onwards). In fact, the specification teaches specific parameters to be associated with the term “percent identity” as applied to the present invention. The specification further provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity (page 372, line 36 to page 373, line 17). This guidance includes a listing of exemplary and preferred substitutions for each of the twenty naturally occurring amino acids (Table 6, page 372). Once such an amino acid sequence was identified, the specifications sets forth methods for making the amino acid sequences ((see page 376, line 9) and methods of preparing the PRO

polypeptides (see Example 140-143). The specification also discloses in detail how to use the claimed polypeptides for various diagnostic or therapeutic purposes. Accordingly, by following such guidelines, one skilled in the art can easily identify and test whether a variant retains the function of PRO1185 and falls within the scope of Claims 121-123. Applicants submit that coupled with the general knowledge available in the art at the time of the invention, the specification provides ample written support for such polypeptides in Example 170, page 539 of the specification. Thus, based on the high percentage of sequence identity and the described method of detecting and quantifying of overexpression in tumor cells, one skilled in the art would have known at the time of the invention, that the Applicants had possession of the claimed polypeptides.

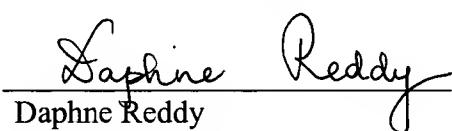
In view of the above, the Examiner is respectfully requested to reconsider and withdraw the rejection of Claims 121-123 for allegedly lacking written support.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-2730P1C42). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

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